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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,450	12/22/2005	Xin Lu	5585-70602-01	6725

4743 7590 03/11/2009

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
03/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,450	LU, XIN	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,7,9,10 and 47-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,7,9,10 and 47-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 16 December 2008 have been entered. Claims 2, 7, 9 - 10, and 47 - 59 are pending and under examination.

Withdrawn Rejections and Objections

2. The following rejections and objections set forth in the previous office action are withdrawn:

A. The objection to the specification is withdrawn in light of the amendments which add sequence identifiers to the text.

B. The rejection under 35 USC 112, first paragraph, for lack of enablement commensurate in scope with the claims is withdrawn in light of the amendments which cancel the subject matter the examiner had considered to be non-enabled.

C. The rejection under 35 USC 112, first paragraph, for lack of adequate written description is withdrawn in light of the amendments which cancel the subject matter the examiner had considered not to be described.

D. The rejection under 35 USC 112, second paragraph is moot as the claims are canceled.

E. The rejection under 35 USC 102(b) is withdrawn in light of the amendments. The claims are now limited to methods comprising contacting samples with antibodies that bind proteins encoded by SEQ ID NO:8 or 9. The prior art reference by Anderson teaches contacting samples with antibodies, but the antibodies are not directed to proteins encoded by these specific nucleic acids.

Maintained Rejections

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 7, 9 - 10, 48, 50 - 56, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Samuels-Lev (Mol. Cell 8:781 – 794, 2001, cited on IDS filed 6 April 2005) in

view of Louis (Journal of Neuropathology and Experimental Neurology 53:11 – 21, 1994, of record).

Independent claims 2 and 50 each are drawn to methods comprising contacting a nerve cell or nerve progenitor cell with an antibody or fragment thereof that binds a polypeptide encoded by SEQ ID NO:8 or 9 (i.e., the proteins of SEQ ID NO:10 and 11) in certain specific samples. The specification discloses (p. 14) that ASPP1 is the protein of SEQ ID NO:10 and is encoded by SEQ ID NO:8, while ASPP2 is the protein of SEQ ID NO:11 and is encoded by SEQ ID NO:9. Samuels-Lev teaches methods of contacting samples comprising cells with antibodies against ASPP proteins; see for example Figure 4E which shows visual evidence of detection, p. 792 last complete paragraph for description of making monoclonal antibodies that bind to ASPP1 and ASPP2 (note this is on point to claims 7 and 56, which recite monoclonal antibodies, and claims 2, 50, and 53 - 54, which are drawn to detection of proteins encoded by SEQ ID NO:8 and 9), and p. 793 second column for description of the protocol of detecting ASPP proteins in cells. The reference teaches methods of using fluorescently-labeled second antibodies (p. 793) for detection, which is on point to claims 9, 10, and 51 - 52, as these are means which enable the detection. Samuels-Lev indicates that mRNA encoding ASPP1 and ASPP2 is decreased in many breast cancers that express wild-type *p53*, suggesting to the artisan of ordinary skill that decreased levels of ASPP1 and ASPP2 protein would be indicative of the presence of cancer in these tissues and that it could be used as a diagnostic tool in tumors that express the wild-type version of the tumor-suppressor p53. Samuels-Lev teaches the artisan of ordinary skill how to make both polyclonal and monoclonal antibodies against ASPP1 and ASPP2; which is on point to claim 55 (see p 792 last complete paragraph). Note claims 48 and 58 are included in this rejection as they use open "comprising" claim language in discussing the antibody fragments; the monoclonal and polyclonal antibodies taught by Samuels-Lev will comprise scFv fragments and "domain antibodies", as these are the parts of the antibody that bind to the antigen. The reference by Samuels-Lev teaches every element of the claimed invention, with the exception that Samuels-Lev does not explicitly teach performing the detection assay with samples comprising either nerve cells or nerve progenitor cells as recited in claim 2. Rather the reference is particularly on point to breast cancer tumors.

Louis teaches that although some types of brain cancer display mutations in p53, many forms of brain cancer do not have such mutations. That is, the cells remain wild-type at the *p53* locus, even though they are tumor cells; see for example p. 16 second column and p. 17. p53

was known to be a tumor suppressor (see Louis), and mutations in this gene (and encoded protein) lead to loss of the tumor-suppressing properties of the protein, resulting in unchecked tumor growth. Louis's teaching that cancerous tumors can be wild-type at the *p53* locus indicates to the artisan of ordinary skill that assays to detect *p53* mutations in samples from these tumors would not be useful to determine if the tissue is in fact cancerous. Rather, the artisan of ordinary skill would understand that other proteins must be used in any assay to diagnose whether or not tissue suspected of being cancerous is in fact cancerous.

It would have been obvious to one of ordinary skill in the art to modify the method of Samuels-Lev and use samples comprising neurons (i.e. nerves) rather than other tissue as taught in the Samuels-Lev reference. The motivation to do so would be to determine if a tumor sample suspected of being cancerous is in fact cancerous, and this motivation comes from the references by Samuels-Lev and Louis. Louis indicates that many brain tumor samples are wild-type at the p53 locus, providing the artisan of ordinary skill a reasonable expectation of success in repeating the steps set forth in Samuels-Lev on brain tumor samples.

Applicant argued, in the remarks filed 16 December 2008, that the artisan of ordinary would not have had a reasonable expectation of success in performing the method as claimed. According to applicant, since the examiner has determined Louis suggests that one should look to levels of "other proteins", and there are between 20,000 - 100,000 proteins, a huge number of possible candidates exist, and nothing in particular points the artisan of ordinary skill to ASPP1 or ASPP2 (SEQ ID NO:10 and 11, encoded by SEQ ID NO:8 and 9 respectively). Applicant also argues that since Samuels-Lev is silent with respect to neurological tumors, an artisan of ordinary skill would have had no motivation to apply the methods from this reference to this class of tumors.

Applicant's arguments have been fully considered but they are not persuasive. While it is true that there are between 20,000 - 100,000 proteins encoded by the human genome, the existence of a large number of possible proteins does not indicate that the claimed method is non-obvious. In fact, the reference by Samuels-Lev clearly focuses attention on ASPP1 and ASPP2, proteins encoded by SEQ ID NO:8 and 9, as those whose expression is altered in certain specific forms of cancer, namely cancers without p53 mutations. Samuels-Lev specifically points out that tumors from many different tissues become cancerous even when p53 is not mutated (see p. 781 first paragraph of Introduction section, which discusses the prevalence of p53 mutations in lung cancer, breast cancer, and leukemia). Additionally

Samuels-Lev teaches that the role of ASPP proteins is to modulate the function of p53 protein (see text in Discussion, particularly beginning at p. 791 first column), indicating that the proteins are likely to have effects on a number of cancers, and not just in breast cancer tumors. Thus, the teachings of Samuels-Lev point the artisan of ordinary skill directly towards these proteins as those that should be investigated for changes in expression in p53-wild-type tumors.

The claimed invention differs from the teachings of Samuels-Lev only in that the starting materials in the claimed invention are nerve cells or nerve progenitor cells, whereas in Samuels-Lev the starting material is breast cancer tissue. Applying the methods disclosed in Samuels-Lev to a different tissue type is not the result of innovation, but of routine experimentation and improvement, particularly in light of the teachings of Louis who indicates that many forms of brain cancer express wild-type p53.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48 and 58 each encompass methods of using a "domain antibody". In the remarks filed 16 December 2008, applicant indicated that support for the new claims can be found at pp. 6 - 9 of the specification. The examiner has found that the paragraph spanning pp. 7 - 8 refers to single domain antibodies, and refers to specific patents which discuss single domain antibodies. However, it is not clear what constitutes a "domain antibody". How many domains must the "domain antibody" have? Which domains must be present?

Amendment to "single domain antibody" would be sufficient to overcome this rejection.

Claim Rejections - 35 USC § 103

5. Claims 2, 7, 9 - 10, 47 - 48, and 50 - 58 rejected under 35 U.S.C. 103(a) as being unpatentable over Samuels-Lev in view of Louis as applied to claims 2, 7, 9 - 10, 48, 50 - 56, and 58 above, and further in view of Hainfeld (U.S. Patent 5,360,895, issued 1 November 1994).

The reasons why claims 2, 7, 9 - 10, 48, 50 - 56, and 58 are obvious over Samuels-Lev in view of Louis are set forth above. However neither of the references explicitly teaches using the particular antigen binding fragments recited in claims 47 and 57.

Hainfeld teaches that Fab fragments of antibodies can be used for detecting cancer; see for example column 1 lines 44 - 48 and column 3 lines 4 - 15. This is on point to claims 47 and 57, as it shows that such fragments were known at the time the present invention was made, and were known to be suitable for diagnostic purposes, particularly for detecting proteins in tumors. However Hainfeld does not teach contacting samples with antibodies that bind to proteins encoded by SEQ ID NO:8 or 9.

It would have been obvious to one of ordinary skill in the art to modify the method rendered obvious by Samuels-Lev in view of Louis by selecting Fab fragments of antibodies for cancer detection, as suggested by Hainfeld. Doing so would have been particularly obvious in view of Hainfeld's teachings that these fragments are suitable for detection, and that the Fab fragments are more able to penetrate tumors than intact antibodies (see Hainfeld column 3 lines 4 - 15). Therefore the particular limitations of claims 47 and 57 are also obvious.

6. Claims 2, 7, 9 - 10, 48 - 56, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Samuels-Lev as applied to claims 2, 7, 9 - 10, 48, 50 - 56, and 58 above, and further in view of Wallace (U. S. Patent 5,646,253, issued 8 July 1997).

The reasons why claims 2, 7, 9 - 10, 48, 50 - 56, and 58 are obvious over Samuels-Lev in view of Louis are set forth above. However neither of the references explicitly teaches using humanized antibodies as recited in claims 49 and 59.

Wallace teaches humanized antibodies against LK26 protein can be used to detect cancer. See for example column 4 lines 4 - 31 for description of how to humanize antibodies and column 3 lines 21 - 27 for description that the humanized antibodies are useful for detecting cancer. This is on point to claims 49 and 59, as it shows that humanized antibodies were known at the time the present invention was made, and were known to be suitable for diagnostic purposes, particularly for detecting proteins in tumors. However Wallace does not teach contacting samples with antibodies that bind to proteins encoded by SEQ ID NO:8 or 9.

It would have been obvious to one of ordinary skill in the art to modify the method rendered obvious by Samuels-Lev in view of Louis by selecting the humanized antibodies for cancer detection, as suggested by Wallace. Doing so would have been particularly obvious in

view of Wallace's teachings that these antibodies are suitable for detection. Therefore the particular limitations of claims 49 and 59 are also obvious.

Conclusion

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
March 10, 2009